REMARKS/ARGUMENTS

Claims 1-19 are pending in the above-referenced application. Claims 1 and 8-11 have been withdrawn from consideration.

Claim 2 has been amended to further define Applicant's invention. New claims 17-19 have been added. Support for the amendment can be found in US publication No. 2007/0071777 of the instant application at, among other places, paragraphs [0037], [0041], [0042] and Table 1. No new matter has been added.

This is a response to the Office Action dated January 5th, 2011 wherein the Examiner rejected claims 2-7 and 12-16 under 35 U.S.C. 103(a) as being unpatentable over EP 391369 (Simon) in view of the "Effects of Postnatal Estradiol and Progesterone Replacement in Extremely Preterm Infants," *The Journal of Clinical Endrocinology & Metabolism*, December 1999 (Trotter) and/or U.S. Patent No. 5,514,673 (Heckenmüller).

Applicant respectfully thanks the Examiner for the time and effort in preparing and issuing the instant Action.

In view of the foregoing claim amendments and the remarks that follow, reconsideration of the rejections and a notice of allowance are respectfully solicited.

§ 103(a) Rejection of Claims 2-7 and 12-16 over Simon et al in view of Trotter and/or in view of Heckenmüller

Claims 2-7 and 12-16 are rejected under 35 U.S.C § 103(a) as being unpatentable over Simon et al in view of Trotter and/or Heckenmüller.

In rejecting the foregoing claims, the Examiner relies on Simon to "teach medicinal oil-in-water emulsions comprising an effective amount of a lipophilic drug". The Examiner alleges that Simon teaches all of the elements of the claimed oil emulsion, except Simon does not teach an emulsion containing progesterone and an estrogen. The Examiner relies on Trotter to teach an oil-in-water emulsion of progesterone and estradiol in a phospholipid-stabilized soybean oil emulsion. The Examiner further relies on Heckenmüller to teach a pharmaceutical composition

for transmucosal administration containing progesterone and/or estradiol, wherein the progesterone and/or estradiol are dissolved in the oil prior to mixing with the aqueous phase. (Office Action, pages 4-5).

Of the rejected claims, amended claim 2 recites:

> 2. (Currently Amended) A hormone-containing isotonic oil emulsion for intravenous administration comprising:
> at least one progestagen and at least one estrogen;
> an oil phase;
> an antioxidant;
> an emulsifier; and
> an aqueous phase;
> wherein the at least one progestagen and the at least one estrogen are dissolved in the oil phase prior to being mixed with the aqueous phase and the oil phase comprises oils of marine origin.

Thus, amended claim 2 is directed to an oil emulsion for intravenous administration comprising, among other things, at least one progestagen and at least one estrogen, an oil phase; an antioxidant; an emulsifier and an aqueous phase. Claim 2 further specifies that the at least one progestagen and the at least one estrogen are dissolved in the oil phase prior to being mixed with the aqueous phase and the oil phase comprises oils of marine origin.

The cited references:

Of the cited prior art, the '369 Simon publication is directed to a pharmaceutical composition suitable for the administration of hydrophobic drugs (page 5, lines 3), including lipophilic drugs such as amphotericin B, narcotic drugs such as morphine-base drugs, hydrophobic benzodiazepines such as diazepam, lipophilic steroids such as progesterone and testosterone propionate, lipophilic polypeptides such as cyclosporine (page 5, lines 4-10). The composition further comprises an oily carrier consisting of mid chain triglyceride (MCT) oil optionally in combination with vegetable oil, a phospholipid, non-ionic and ionic surfactants and optionally an anti-oxidant such as α-tocopherol (Abstract, page 3, line 35, page 5, line 2). Simon explicitly teaches that MCT oil is the oily carrier of choice because "MCT oil has many advantages over vegetable oil", including "lower susceptibility to oxidation, having a specific

density of 0.94-0.95 which is higher than that of vegetable oil and which is close to that of water thus facilitating the obtaining of a stable emulsion; being less hydrophobic than vegetable oil and therefore enables achieving higher concentrations of the drug dissolved therein; having a lower viscosity which again enables obtaining a higher concentration of the oily phase in the composition without substantially increasing its viscosity" (Simon, page 3, line 55 to page 4, line 5). Simon does not disclose or suggest an oil phase of marine origin and teaches away from using vegetable oil.

As acknowledged by the Examiner, Simon does not teach an emulsion comprising progesterone and an estrogen. The Examiner relies on Trotter et al. to teach an oil-in water emulsion comprising estradiol and progesterone. The Examiner further relies on Heckenmüller et al to teach a pharmaceutical composition for transmucosal administration containing progesterone and/or estradiol, wherein the progesterone and/or estradiol are dissolved in the oil prior to mixing with the aqueous phase (Office Action, page 4).

Trotter et al. describe a hormone replacement solution for use in extremely preterm infants (Abstract). Trotter teaches diluting 17-β-estradiol and progesterone in 98% ethanol and mixing the solution with a phospholipid-stabilized soybean oil emulsion such as Intralipid (Pharmacia & Upjohn, Inc.) for parenteral administration (page 4532, first column, last paragraph). Intralipid[1] from Pharmacia & Upjohn contains purified soybean oil, purified egg phospholipids and glycerol in water. As described, the hormones 17-β-estradiol and progesterone are diluted in 98% ethanol before being added to Intralipid. As Trotter specifically teaches dissolving estradiol and progesterone in an aqueous phase (98% ethanol) before mixing the solution with Intralipid, Trotter teaches away from claim 2, which recites in part "wherein the at least one progestagen and the at least one estrogen are dissolved in the oil phase **prior** to being mixed with the aqueous phase" (emphasis added). Trotter does not disclose or suggest any oil phase other than the soybean oil emulsion Intralipid.

[1] http://www.rxmed.com/b.main/b2.pharmaceutical/b2.1.monographs/CPS-%20Monographs/CPS-%20(General%20Monographs-%20I)/INTRALIPID.html

The '426 Heckenmüller publication is directed to a composition suitable for the transmucosal (e. g. nasal route) administration of the natural human sex hormones 17-β-estradiol or progesterone (Heckenmüller, page 4, lines 11-14).

Heckenmüller teaches dissolving the hormones 17-β-estradiol and/or progesterone in an oil phase before mixing it with the water phase (Heckenmüller, page 5, lines 21-24). Heckenmüller teaches that "artificial or natural oils or mixtures thereof can be used", but discloses only middle chain triglycerides, such as "caprylic/capric triglycerides and mixtures thereof" (Heckenmüller, page 4, line 32, page 6, lines 16-18). All the examples provided use Miglyol® 812N[2] (Heckenmüller, pages 7-9), which is a neutral oil of middle chain caprylic and capric triglycerides. Heckenmüller specifically emphasizes that the solubility of the hormones in the oil phase is an important factor, and that the oil or oil mixtures "are characterized in that the solubility for estradiol must be at least 0.5% by weight and for progesterone at least 2%" (Heckenmüller, page 6, lines 8-10). Heckenmüller does not disclose or suggest any oil phase other than middle chain triglycerides.

The cited references fail to render the pending claims obvious under § 103(a):

Applicant respectfully submits that, contrary to the Examiner's assertion, the cited references are not combinable, as at least two of them teach away from the claimed emulsion. Furthermore, even if erroneously combined, the cited references still fail to disclose all of the elements of the claimed emulsion and therefore fail to render it obvious under § 103(a).

Of the cited references, as set forth above, Trotter specifically teaches dissolving estradiol and progesterone in an aqueous phase (98% ethanol) before mixing the solution with Intralipid. By teaching dissolving the hormones estradiol and progestagone in 98% ethanol before adding it to the oil phase (Intralipid), Trotter teaches away from the claimed emulsion, which recites "wherein the at least one progestagen and the at least one estrogen are dissolved in the oil phase **prior** to being mixed with the aqueous phase" (emphasis added). "A reference may be said to

[2] http://abstracts.aapspharmaceutica.com/expoaaps07/Data/EC/Event/Exhibitors/263/cb63fb76-28f4-4948-a6d0-ae249dae9c30.pdf

teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. In *re Gurley*, 27 F. 3d 551, 553 (Fed. Cir. 1994)".

Even though the Examiner merely relies on Trotter to disclose an estrogen, "a prior art reference must be considered in its entirely, i.e., as a whole, including portions that would lead away from the claimed invention" (§ MPEP 2141.02 (VI)). As Trotter teaches away from the claimed emulsion, Trotter cannot be combined with any other references to render the claimed emulsion obvious, as "[i]t is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)." § MPEP 2145.

Furthermore, by teaching that the natural sex hormones progesterone and estradiol have very limited effectiveness when taken orally, and intravenous or intramuslar administration of these sex hormones is inconvenient and carries a potential risk for infections (Heckenmüller, page 1, line 38 to page 2, line 10), Heckenmüller discourages a skilled artisan from administering the natural sex hormones intravenously. Thus, Heckenmüller also teaches away from the claimed emulsion.

Notwithstanding the fact that two of the cited references teach away from the claimed emulsion and therefore the combination of the cited references is defective, even if erroneously combined, the cited references still fail to disclose or suggest all the elements of the claimed emulsion. At a minimum, Simon and Trotter and/or Heckenmüller do not disclose a hormone-containing isotonic oil emulsion comprising at least one progestagen and at least one estrogen, wherein the at least one progestagen and the at least one estrogen are dissolved in the oil phase prior to being mixed with the aqueous phase and the oil phase comprises oils of marine origin, as recited in part by claim 2. As the cited references fail to disclose all of the elements of the claimed emulsion, they fail to render claim 2 obvious under § 103(a).

Furthermore, Applicant respectfully submits that from the teachings of the cited references, a person of ordinary skill in the art would not have been motivated to arbitrarily incorporate an oil phase comprising oils of marine origin to produce the claimed emulsion.

"[T]he test [for obviousness] is what the combined teachings of the references would have suggested to those of ordinary skill in the art." Sovich, 769 F. 2d at 742-43.

As well known to one of ordinary skill in the art, and as described in the instant specification, medium or middle chain triglycerides (MCT) do not contain any unsaturated fatty acids and thus they contain neither ω-6 nor ω-3 fatty acids (instant specification as published in the '777 Publication, [0040]). In contrast, both vegetable oils and marine oils contain high amount of polyunsaturated fatty acids. Vegetable oils are characterized by a high content of polyunsaturated fatty acids of the ω-6 series while their content of ω-3 fatty acid is low ('777 Publication, [0038]). On the other hand, marine oils, including fish oils, are characterized by a high content of polyunsaturated fatty acids of the ω-3 series while their content of ω-6 fatty acid is low ('777 Publication, [0041]).

As set forth above, Simon explicitly teaches that "MCT oil has many advantages over vegetable oil", because among other things MCT oil, having no unsaturated fatty acids, is less susceptible to oxidation, and therefore more stable than vegetable oil. According to Simon, MCT oil having shorter chain lengths (from C_6 to C_{14}), and being less hydrophobic, therefore can allow a higher solubility of the drugs or hormones to be dissolved. Simon also teaches that MCT oil also has a lower viscosity and therefore allows for a higher concentration of the oily phase in the composition (Simon, page 3, line 55 to page 4, line 5). Thus, from the teachings of Simon, a skilled artisan would have been discouraged from using oils which are high in unsaturated fatty acids or longer in chain lengths, such as oils of marine origin including fish oils, which typically comprise long chains of polyunsaturated fatty acids such as eicosapentaenic acid (EPA, 20:5) and docosahexaenic acid (DHA, 22:6) ('777 Publication, [0041]) .

Heckenmüller also emphasizes that the solubility of the hormones in the oil phase is an important factor, and consistently with Simon's teachings, teaches primarily the use of middle chain triglycerides in the preparation of the transmucosal formulation of the sex hormones progesterone and/or estradiol (Heckenmüller, page 4, line 32, page 6, lines 16-18 and pages 7-9). Thus, from the teachings of Heckenmüller, a skilled artisan would have been discouraged from using oils which may reduce the solubility of the hormones progesterone and/or estradiol, such

as oils of marine origin including fish oils, which typically comprise long chains of polyunsaturated fattey acids.

As set forth above, oils of marine origin, including fish oils, and vegetable oils have a high content of polyunsaturated fatty acids. Marine oils and vegetable oils are also much longer in length than MCT oils. Thus, from the teachings of both Simon and Heckenmüller, a skilled artisan would not have been motivated to modify the cited references to produce the claimed emulsion.

For at least the reasons set forth above, Applicant respectfully submits that the cited references of Simon and Trotter and/or Heckenmüller fail to render claim 2 obvious under § 103(a). Since claims 3-7 and 12-16 depend from claim 2, they too are allowable over the cited reference for at least the same reasons.

New claims 17-19:

New claims 17-19 depend directly or indirectly from claim 2. Therefore, they are allowable over the cited references for at least the same reasons.

CONCLUSION

In view of the foregoing amendments and arguments. Applicant respectfully submits that claims 2-7 and 12-19 are patentable and allowance is respectfully solicited.

Should the Examiner wish to speak with Applicant's agent, she is invited to contact the undersigned at the telephone number identified below.

Respectfully submitted,
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